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DOSSIER
Alcohol Ethoxysulphates (AES)

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Human & Environmental Risk Assessments on ingredients of European household cleaning products:

Alcohol Ethoxysulphates (AES): Human Health Risk Assessment

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Alcohol Ethoxysulphates (AES): Environmental Risk Assessment

1. Substance Characterisation

Alcohol ethoxysulphates (AES), also known as alkyl ethersulphates, are a widely used class of anionic surfactants. They are used in household cleaning products, personal care products including toothpaste and shampoos, hand and other personal cleaning products, institutional cleaners and industrial cleaning processes, and as industrial process aids in emulsion polymerisation and as additives during plastics and paint production. Uses in household cleaning products, relevant to the HERA program of risk assessments, include laundry detergents, hand dishwashing liquids, and various hard surface cleaners.

1.1. CAS No and Grouping information

There are more than 36 CAS Numbers describing AES. A comprehensive list is presented in Appendix 1 of this document. Although clearly important from a Regulatory perspective, this assessment is not based on CAS Nos., but on a clear definition of the product family's composition.

1.2. Chemical structure and composition

The alcohol ethoxysulphate family is defined for HERA purposes to encompass commercial grades of linear-type primary alcohol ethoxysulphates containing AES components of basic structure $C_nH_{2n+}O(C_2H_4O)_mSO_3X$) where n=10-18 and m = 0-8 and X = sodium, ammonium or triethanolamine (TEA). Sodium salts of AES are by far the commonly used grades.

2.2 Hazard Assessment

2.2.1. Summary of the available toxicological data

2.2.1.1. Acute Toxicity

2.2.1.1.1. Acute Oral Toxicity

The acute oral toxicity of alcohol ethoxysulphates (AES) was evaluated with rats in several acute oral toxicity studies [Hüls AG, 1997a; Hüls AG, 1986a; Shell Research Ltd. 1975a; Shell Research Ltd., 1978a; Shell Research Ltd., 1978b; Brown, V. et al., 1968; Shell Research Ltd., 1975b; Shell Research Ltd., 1978c; Shell Research Ltd., 1975c; Shell Research Ltd., 1972; Brown, V. et al., 1970; Shell Chemical Co., 1967; Arthur D. Little, 1991]. The test materials were typically AES solutions containing 25 – 70% active material. The dilutions were administered at doses ranging from 2.5 – 10 ml/kg bodyweight. Most of the studies pre-date Good Laboratory Practice (GLP) regulations and in only one of these [Vermeire et al., 1993], the study design included at least 5 animals of each sex per dose group, thus meeting the critical aspect of current testing standards as defined in OECD methodologies. In these studies, the LD50 was estimated to be > 1.3 g active material per kg bodyweight. In a review for the Soap and Detergent Industry Association, Arthur D. Little reported rat oral LD50 values ranging from 1.7 - > 5 g/kg bodyweight [Arthur D. Little, 1991]. The most reliable studies will be discussed in the following paragraph in more detail.

A recent study [Hüls AG, 1997a] which was rated as reliable without restrictions according to the Klimisch criteria [Klimisch et al. (1997)], followed the guidelines of OECD method 401 and was compliant with GLP, a group of ten rats, five of each sex, was given a single oral dose of the triisopranolammonium salt of C12-14AE2S (90% active material) at a dose level of 2000 mg/kg bodyweight. The undiluted liquid was administered by gavage with an application volume of 2 ml/kg bodyweight. The rats were observed daily for any mortalities and clinical symptoms following treatment. Individual body weights were recorded on days 0 (prior to dosing), 7 and 14. At the end of the 14-day observation period, the animals were sacrificed and macroscopically examined. There were no deaths following a single oral application of the tested AES. The animals showed mild clinical symptoms such as increased activity and piloerection as a reaction to the treatment for approximately four hours after dosing. The macroscopic examination on day 14 showed no significant lesions. In conclusion, the acute lethal oral dose to male and female rats of the tested AES was found to be > 2 g/kg.

In a further study, rated as reliable with restrictions according to the Klimisch criteria, was also conducted according to the guidelines of OECD method 401, but not following GLP standards, a 70% solution of NaC12-14AE2S was administered by oral gavage at a dose level of 2.5 g/kg. No mortalities occurred under the dosing conditions. The rats achieved acceptable bodyweight gains throughout the study and showed mild clinical signs (unkempt fur, abdominal position, diarrhoea) as a reaction to the treatment for approximately 2 hours after dosing. The macroscopic examination on day 14 showed no significant lesions.

Conclusion

Alcohol ethoxysulphates are considered to have a low order of acute oral toxicity in the rat. In two recent and guideline compliant acute oral toxicity studies with marketed AES substances, the

LD50 was greater than 2000 mg/kg bodyweight. The clinical findings such as increased activity and piloerection following oral exposure are indicative of gastrointestinal stress and could be explained by the irritant nature of the test solutions under the conditions of oral gavage.

2.2.1.1.2. Acute Inhalation Toxicity

There are no test data available to evaluate the acute inhalation toxicity of AES. Only one study was identified in the review conducted by Arthur D. Little. In this study, rats (group size not specified) survived a 1 hour exposure to 60 mg/l of 59% active material solution of NH_4 C12-14AE3S. No additional details are available.

Conclusion

Given the lack of information on the study protocol and study results, this study is not suitable to assess the acute inhalation toxicity hazard of AES-type surfactants.

2.2.1.1.3. Acute Dermal Toxicity

The acute dermal toxicity of AES has been evaluated in several rat studies [Hüls AG, 1997b; Shell Research Ltd. 1975a; Shell Research Ltd., 1978a; Shell Research Ltd., 1978b; Shell Research Ltd., 1975b; Shell Research Ltd., 1978c; Shell Research Ltd., 1975c; Shell Research Ltd., 1972; Shell Chemical Co., 1967; Arthur D. Little, 1991] and in one rabbit study [Shell Chemical Co., 1967]. Most of the studies did not follow OECD guidelines (e.g. use of small group sizes) and did not comply with GLP regulations However, despite some protocol deficiencies, the studies were reported in sufficient detail to allow a reasonable assessment of the potential dermal toxicity of AES in laboratory animals. The investigations included mortality and clinical observations. No mortality was observed in the rat studies at the dose level tested and subsequently LD50 values were expressed to be above the highest investigated dose levels, *i.e.*, >0.65 g/kg [Shell Research Ltd., 1978a], >1.12 g/kg [Shell Research Ltd., 1978b], >2.4 g/kg [Shell Research Ltd. 1975a], >1.25 g/kg [Shell Research Ltd., 1972], >1.08 g/kg [Shell Research Ltd., 1975b], >0.54 g/kg [Shell Research Ltd., 1978c], >1.8 g/kg [Shell Research Ltd., 1975c] and 4.6 g/kg [Shell Chemical Co., 1967]. Arthur D. Little, 1991 reported dermal LD50 values for AES on both intact and abraded rabbit skin ranging from 4 – 12 g/kg bodyweight. At highest dosage levels, various degrees of skin irritation (moderate to severe erythema and oedema) were reported and signs of intoxication included sporadic signs of haemorrhage around the eyes and nose, piloerection, and diarrhoea.

An acute dermal toxicity study (limit test) following OECD method 402 and complying with GLP guidelines was performed to assess the acute dermal toxicity of triisopranolammonium salt of C12-14AE2S (90% active material) in the rat. A group of ten rats, five of each sex, was given a single dermal application of the test substance at a dose level of 2 g/kg bodyweight. There were no deaths and no signs of systemic reaction to the treatment. Following removal of the dressing, moderate to severe dermal irritations indicated by inflammation of the epidermis and eschar formation were observed at the treatment site. The effects cleared over time. Some minor residual skin lesions were observed in 1 animal at the end of the 14-day observation period. No

abnormalities were recorded at the macroscopic examination on day 14. The acute lethal dermal dose to male and female rats of NH_4C12-14AE2S was determined to be > 2 g/kg bodyweight.

Conclusion

Alcohol ethoxysulphates are considered to be of low acute dermal toxicity to rats. This was demonstrated in a recent, OECD guideline and GLP compliant acute dermal toxicity limit test in rats. This study has been judged to provide reliable information on the dermal toxicity of AES.

This assessment is supported by a substantial number of further acute dermal toxicity studies in rats and rabbits with a lower reliability score, which also demonstrated low acute dermal toxicity of AES-type surfactants.

2.2.1.1.4. Skin Irritation

Several skin irritation studies were conducted on rabbits considering different concentrations (0.1%, 1%, 10%, neat material), exposure duration (4h, 24h, 36 h) and exposure conditions (open application, semi-occlusion, full occlusion) [Hüls AG, 1997c; Hüls AG, 1986b; Shell Research Ltd., 1978d; Shell Research, Ltd., 1978e; Shell Oil Co., 1989; Shell Research Ltd. 1975a; Shell Research Ltd., 1978a; Shell Research Ltd., 1978b; Shell Research Ltd., 1968; Shell Research Ltd., 1978c; Shell Research Ltd., 1975c; Brown et al., 1970, Shell Chemical Co., 1967; Arthur D. Little, 1991, Hüls AG, 1997b.

The triisopranolammonium salt of C12-14AE2S (90% active material) was tested in an EC standard (4h) skin irritation study on rabbits [Hüls AG, 1997b]. The study followed OECD method 404 and was in compliance with GLP regulations. In this study, the undiluted liquid test substance was applied in a single dose for 4 hours to the shorn intact skin of three animals. The administration of the test substance led to well-defined erythema 24 hours after application, and was associated with distinct oedema in two animals and severe oedema in the 3rd animal. Forty–eight (48) hours after application, these signs of irritation were still well-defined and without change in 2 out of 3 animals. The 3rd animal presented with moderately severe erythema, associated with severe oedema, dry skin and scaling, 48 hours after application. Seventy-two (72) hours after application, 2 animals exhibited localized skin irritation in the form of well-defined or moderately severe erythema and oedema, and 1 rabbit had slight subcutaneous haemorrhages. On the 14th day after administration of the test substance, the skin of all the animals was free from signs of irritation. For all 3 animals, an erythema/eschar mean score of 2.33 and an oedema mean score of 2.78 was determined. This score indicates moderate skin irritation properties of the undiluted test substance.

In two further studies [NOTOX, 1994, Hüls AG, 1986b], NaC12-14AE2 (70% active material) was tested in the EC standard irritation test. Both studies were conducted in compliance with OECD method 404, but only 1 complied with GLP regulations [NOTOX, 1994]. As in the case of the study discussed before, exposure to the test substance for 4 hours resulted in moderate to severe erythema and oedema. After 72 hours, reduced flexibility, fissuring of the skin and severe erythema and oedema were apparent. One study [Hüls AG, 1986b] terminated the observations at the 14th observation day and clinical signs of irritation were still apparent at this time. In the other study [NOTOX, 1994], animals were observed for 21 days and irritation had completely resolved within 21 days after exposure, but patches of bold skin persisted at termination.

As indicated before, further studies were conducted to investigate the skin irritation of effects of various dilutions of AES at different exposure durations and conditions. These studies were investigative in nature and neither was in compliance with OECD guidelines, nor with GLP regulations. However, these studies provide useful information on AES exposure conditions that are of particular relevance in consumer product applications. In 4hr or 24hr skin irritation studies on rabbits, a 0.1% AES solution did not show any signs of irritation, a 1% AES solution showed slight irritation, and solutions containing AES of 10 – 30% were mildly to moderately irritating under the patch conditions of the animal test.

Conclusion

The irritation potential of AES is concentration dependent. Materials with concentrations higher than 70% are moderately to severely irritating to rabbit skin under the conditions of the EC irritation test, and therefore classified as irritating to skin according to EU criteria as laid down in the Dangerous Substance Directive (67/548/EEC). At concentrations between 10 and 30%, the AES solutions exhibit mild to moderate irritancy under the conditions of an occluded patch test. AES concentrations below 1% are virtually non-irritating under the conditions of the acute skin irritation testing protocol.

2.2.1.2. Eye Irritation

The potential of AES to cause eye irritation under accidental exposure conditions has been evaluated in several rabbit eye irritation studies [Hüls AG, 1997d; Hüls AG, 1986c, Shell Research Ltd. 1975a, Shell Research Ltd., 1978b, Shell Research Ltd., 1975b, Shell Research Ltd., 1978c, Shell Research Ltd., 1972, Brown et al., 1970, Arthur D. Little, 1991]. Most of the studies with undiluted or concentrated AES solutions (e.g. 32.6% C9-11AE2.5S, 70% C12-13AE2S, 28% C12-13AE2S) resulted in extensive corneal damage, inflammation of the iris and maximal conjunctival irritation with no significant improvement seen over a 7-day recovery period after product administration [Shell Research Ltd. 1975a Shell Research Ltd., 1975b, Brown et al., 1970]. In the same studies, which were neither conducted according to OECD guidelines (e.g., protocol deviations such as application volume and observation period), nor followed the principles of GLP, the authors also investigated the same materials at concentrations of 10%, 1% and 0.1%. Generally, solutions containing 10% AES were observed to cause moderately irritating effects while 1% and 0.1% dilutions were virtually non-irritating. The most reliable studies will be discussed in the following paragraph in more detail.

The triisopranolammonium salt of C12-14AE2S (90% active material) was tested in an acute eye irritation study ("Draize test") according to OECD method 405 and following the principles of GLP. In this study, 0.1ml of the liquid test substance was administered into the conjunctival sac of one eye of each of the 3 rabbits. After an exposure time of 24 hours, the eyes were flushed with warm physiological saline. Twenty-four hours after exposure, the animals were observed to have reactions of the conjunctivae in the form of diffuse crimson red discoloration (individual blood vessels not easily discernible), together with distinct swelling and partial eversion of the eyelids. The cornea was slightly opaque over the entire surface, and the iris of one animal showed severe hyperaemia. Up to 72 hours after administration, these signs of irritation were largely unchanged and after 6 days, all signs of irritation began to diminish. After day 17, 2 animals were free from signs of irritation of the eye and mucosa. The 3rd animal was cleared after 24 days.

In another study, 28% active C12-14AE2S was also tested in the Draize test, following the guidelines specified in the OECD method 405. GLP compliance was not mentioned. Again, in this study the tested AES material caused corneal opacity, iritis and conjunctivitis in all test animals. While the conjunctivitis appeared to improve in all 3 test animals approximately 8-10

days after exposure to the test material, corneal opacity and the circumcorneal injection in the iris were still present in 2 animals after 21 days.

Further investigative studies were conducted to determine the effect of rinsing and AES alkyl chain length on the eye irritation potential in rabbits [Procter & Gamble, 1996b]. It was found that rinsing after instillation greatly reduced the severity of eye effects and that AES in the C12-16 range produced more severe effects than AES with longer or shorter chains. This was primarily manifested by longer clearing times (> 7 days versus 1-7 days).

Conclusion

In two independent OECD and GLP compliant acute eye irritation studies, the triisopranolammonium salt of C12-14E2S (90% active material) and NaC12-14E2S (28% active material) were shown to be moderately to severely irritating to rabbit eyes. Due to its persistent effects, these materials were to be classified as severely irritating, according to the EU criteria as laid down in the Dangerous Substance Directive (67/548/EEC).

In studies with a lower reliability score it was shown that solutions containing less than 1-10% AES are slightly to moderately irritating to eyes and below 1%, AES solutions are virtually non-irritating.

2.2.1.3. Skin Sensitization

The skin sensitization potential of AES was evaluated in the guinea pig maximization test according the Magnusson-Kligman protocol [Hüls AG, 1989; Henkel KGaA, 1977a; Henkel KGaA, 1985; Henkel KGaA, 1977b; Shell Research Ltd., 1975d; Shell Research Ltd., 1980a; Shell Research Ltd., 1983a, Shell Research Ltd. 1975a, Shell Research Ltd., 1978a, Shell Research Ltd., 1978b, Shell Research Ltd., 1975b, Shell Research Ltd., 1978c, Shell Research Ltd., 1978d, Shell Research, Ltd., 1978e] and in the non-adjuvant Buehler protocol in guinea pigs [Hüls AG, 1997e, Shell Research Ltd., 1975b, Shell Research Ltd., 1972, Brown et al., 1970, Arthur D. Little, 1991]. Further results of skin sensitization studies are listed in a review conducted for the US soap and detergent industry [Arthur D. Little, 1991].

In summary, of 15 studies conducted on different AES batches and materials according to the Magnusson-Kligman protocol, 14 studies revealed no evidence for skin sensitization potential of AES and only 1 study resulted in a positive result, indicating weak sensitization potential of a tested AES batch. Of the available 8 Buehler studies, 6 studies did not indicate any skin sensitization potential of the tested AES batches and 2 studies resulted in a weak positive response. It must be noted that the majority of the available studies were not conducted according to the OECD guideline protocols, nor according GLP standards. Nevertheless, based on the limited information available, these studies appear to be scientifically well conducted and the results should be included in the overall evaluation. The studies reported in most detail will be discussed in the following paragraphs.

NaC12-14AE2S (28% active material) was evaluated in the Magnusson-Kligman guinea pig maximization test [Hüls AG, 1989] according to OECD method 406. In the induction phase, the treatment group was injected on day zero 3 pairs of 0.1ml volume (injection 1: a 1:1 mixture

Freunds' complete adjuvant (FCA) and water; injection 2: 0.1% test substance in water; injection 3: 0.1% test substance in a 1:1 mixture FCA) in the shoulder region of female guinea pigs. A week later, a patch containing 30% solution of the test substance was placed over the injection area for 48 hours in the treatment group. The control groups were treated in the same manner, but without the test substance (i.e., 3 injections on day 0 and patch application on day 7). Two weeks after the induction phase, the flanks of the treated and the control animals were cleared of hair and an occlusive 'challenge' patch containing 10% of the test substance (or water in case of the control group) was applied to one flank of the animals for 24 hours. Approximately 48 and 72 hours from the start of the challenge application, the skin reaction was observed and recorded according to the Magnusson-Kligman grading scale. Under the test conditions, NaC12-14AE2S did not cause skin sensitization in guinea pigs.

Further AES materials such as NaC12-14AE2S (27% active material) and a mixture of sodium laureth sulphate, sodium laureth-8 sulphate and sodium oleth sulphate (5-10EO, 29% active matter) were evaluated according the same protocol and were found to not cause skin sensitization in guinea pigs [Henkel KGaA, 1977a, Henkel KGaA, 1977b]. However, one batch of NaC12-15E3S caused a weak skin sensitization response [Henkel KGaA, 1985]. In this study, 20 animals were induced intradermally with a 0.25% aqueous solution of the test item and complete Freund' adjuvant. One week after, an occluded patch containing 50% solution of the test substance was placed over the injection area for 48 hours. After a 14 day rest period, the test animals were challenged with an occluded patch containing a 20% solution of the test substance. 24 and 48 hours after removal of the challenge patch, dermal reactions (score 1) were seen in seven animals. A rechallenge was performed seven days later by applying a 10% aqueous solution of the test substance on the flanks opposite to the treatment area. Two out of twenty animals displayed weak skin effects (score 1).

In a more recent study, the triisopranolammonium salt of C12-14AE2S was tested according the Buehler method in guinea pigs following OECD guidelines 406 and in compliance with GLP standards [Hüls AG, 1997e]. To determine the potential sensitizing effect of this test substance, 20 test animals and 10 control animals were tested with the highest readily tolerated concentration of the test substance, which led to slight to well-defined signs of irritation. A 50% strength formulation was used for treatment during induction phases I, II, and III and a 25% strength formulation of the test substance was administered as the highest non-irritant concentration during challenge. The challenge treatment did not cause any cutaneous reactions in the form of erythema or oedema on the posterior right flank of any treated animal in the test and control groups 30 and 54 hours after administration. Based on these results, the test material NH4C12-14E2S showed no sensitizing effect on guinea pigs under the described test conditions.

In 1966, skin sensitization associated with exposure to ethoxysulphates was reported in Norway. Walker et al., 1973 conducted a series of investigations to determine the source of this response and identified a contaminant in one particular AES batch shown to be the responsible sensitizing agent. Connor et al., 1975 identified the contaminant in AES to be 1-dodecene-1,3-sultone, 1-tetradecene-1,3 sultone, 2-chloro-1,3 dodecene sultone and 2-chloro-1,3-tetradecene sultone. Connor et al. demonstrated that these sultones could be formed only under very specific, extreme AES manufacturing conditions. It became evident that the unsaturated and the chloro-sultones which are considered to be potent skin sensitizers were the result of conditions not normally

present and readily avoidable in AES manufacture. The formation of sultones in the AES production is to date not an issue anymore. Presently, residual levels of unsaturated and chloro-sultones and their precursors are monitored in AES batches on a routine basis.

Conclusion

Taking a weight of evidence approach and considering quality criteria (*i.e.,* compliance with OECD methods, GLP) in evaluating reliability of individual studies, AES are not considered to be a skin sensitizers. The vast majority of available guinea pig studies in which AES was tested for skin sensitization properties demonstrated the absence of skin sensitizing potential of AES. Only a few studies indicated a weak sensitization potential of AES, but it should be taken into consideration that observed reactions may have been confounded with irritation reactions.

2.2.2. Repeated Dose Toxicity

2.2.2.1. Oral route

NaC12-15AE3S was tested at doses of 0%, 0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1% and 1.5% in a 3-week dietary rat feeding study [Unilever, 1979a]. Three (3) animals per sex per dose and 6 animals of each sex in the control group were used. In summary, the organ most affected by the feeding of NaC12-15AE3S was the liver. No effects were observed in rats fed at 0.188% dietary level (254 mg/kg/body weight per day) and less. The lowest observed effect level, based on hepatocytic hypertrophy was 0.375% which is equivalent to 487 mg/kg body weight per day. Significantly increased organ weights (liver, kidney, brain) were observed in males and females at doses equal (females) or higher (males and females) than the LOEL established for hepatocytic hypertrophy.

NH4C12-15E3S was tested at doses of 0%, 0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1% and 1.5% in a 3-week dietary rat feeding study [Unilever, 1979b]. Three (3) animals per sex per dose and 6 animals of each sex in the control group were used. In summary, the only organ affected by the feeding of NH4C12-15E3S was the liver. No effects were observed in rats fed at 0.188% dietary level (232 mg/kg/body weight per day) and less. The lowest observed effect level, based on significant increases in plasma alkaline phosphatase activity, was 0.375% which is equivalent to 465 mg/kg body weight per day. Significantly increased liver weight was observed in males and females at doses higher than the LOEL established for the change in some plasma enzyme levels.

NaC12-15E3S containing 21.1% ethanol and 1.15% methanol (note: after mixing with the diet and storage for 3-4 days methanol was no longer detectable and more than 98% of remaining ethanol was evaporated) was tested at doses of 0%, 0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1% and 1.5% in a 3-week dietary rat feeding study [Unilever, 1980a]. Three (3) animals per sex per dose and 6 animals of each sex in the control group were used. In summary, the organ mostly affected by the feeding of NaC12-15E3S was the liver. No effects were observed in rats fed at 0.094% dietary level (108 mg/kg/body weight per day) and less. The lowest observed effect level, based on significant increases in plasma alkaline phosphatase activity, was 0.188% which is equivalent to 217 mg/kg body weight per day. Significantly increased liver weight was

observed in males and females at doses equal (females) or higher (males and females) than the LOEL established for the change in some plasma enzyme levels.

NH4C13-15E3S was tested at doses of 0%, 0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1% and 1.5% in a 3-week dietary rat feeding study [Unilever, 1979c]. Three (3) animals per sex per dose and 6 animals of each sex in the control group were used. In summary, the organ mostly affected by the feeding of NH4C12-15E3S was the liver. No effects were observed in rats fed at 0.375% dietary level (461 mg/kg/body weight per day) and less. The lowest observed effect level, based on hepatocyte hypertrophy, was 0.75% which is equivalent to 857 mg/kg body weight per day. Significantly increased organ weights (liver, brain, testes) were observed in males and females at doses higher than the LOEL established for hepatocytic hypertrophy.

NaC12-14E3S was tested at doses of 0%, 0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1% and 1.5% in a 3-week dietary rat feeding study [Unilever, 1979d]. Three animals per sex per dose and six animals of each sex in the control group were used. In summary, the only organ affected by the feeding of NH4C12-15E3S was the liver. No effects were observed in rats fed at 0.094% dietary level (120 mg/kg/body weight per day) and less. The lowest observed effect level, based on increase in plasma levels of glutamic-pyruvic transaminase and alkaline phosphatase, was 0.188% which is equivalent to 236 mg/kg body weight per day. Significant changes in organ weights (liver, kidney, heart, adrenals) were observed in males and females at doses higher than the LOEL established for changes in plasma enzyme levels.

NaC16-18E4S was tested at doses of 0%, 0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1% and 1.5% in a 3-week dietary feeding study [Unilever, 1980b]. Three (3) animals per sex per dose and 6 animals of each sex in the control group were used. In summary, the organ mostly affected by the feeding of NH4C12-15E3S was the liver. No effects were observed in rats fed at 0.375% dietary level (468 mg/kg/body weight per day) and less. The lowest observed effect level, based on hepatocyte hypertrophy and increases in plasma levels of glutamic-pyruvic transaminase, was 0.75% which is equivalent to 969 mg/kg body weight per day. Significant changes in organ weights (liver, kidney, heart) were observed in males and females at doses higher than the LOEL established for changes in plasma enzyme levels.

NaC12-15E3S was tested at doses of 0%, 0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1% and 1.5% in a 3-week dietary rat feeding study [Unilever, 1979e]. Three (3) animals per sex per dose and 6 animals of each sex in the control group were used. In summary, the organ mostly affected by the feeding of NH4C12-15E3S was the liver. No effects were observed in rats fed at 0.375% dietary level (441 mg/kg/body weight per day) and less. The lowest observed effect level, based on hepatocyte hypertrophy, was 0.75% which is equivalent to 872 mg/kg body weight per day. Significant changes in organ weights (liver, brain, heart, spleen) were observed in males and females at doses higher than the LOEL established for hepatocyte hypertrophy.

The Unilever studies summarized above were not conducted according to OECD and GLP guidelines. However, the methodology used was similar in many respects to OECD Guideline No. 407.

In a 28-day oral gavage rat study, a blend of alkyl (C14-18) sulphate and C12-13E6.5S was tested at 30, 100, 300, and 1000 mg/kg/day [Shell Oil, 1992]. This blend caused irritation to the forestomach of the test animals, evidenced as hyperplasia and hyperkeratosis. Histologically, the hyperplasia appeared as a thickening of the non-glandular stomach epithelium at 100, 300, and 1000 mg/kg/day, but not at 30 mg/kg/day. Similar to the 90-day oral gavage study discussed above, the effects observed in forestomach are considered to be local treatment-related and concentration dependent irritant effects. Since there is no human equivalent to the rat forestomach, these effects are not considered to be relevant to human health assessment. No further information is available on this study and thus, a NOEL or NOAEL for systemic toxicity could not be established.

Synthetic NaC12-15AE3S and natural NaC12AE3S were tested in a 90-day rat diet study at dose levels of 0, 40 200, 1000 and 5000 ppm active material [Walker, 1967]. Health, behaviour, body weight, food intake, haematological and urinary parameters remained within normal limits at all doses. Total serum protein was increased in males in the 5000ppm dose group of NaC12-15AE3S. Differences in absolute organ weights were observed at 5000ppm only. Both ethoxysulphates increased kidney weight in males. Liver weight was increased at 5000ppm in both sexes by NaC12-15AE3S. Females receiving NaC12AE3S showed increased liver, kidney and heart weights. A large variation was reported in male heart weights in rats receiving 1000ppm of NaC12-15AE3S, but the increase was not considered to be treatment related. No increase in heart weight was reported for males receiving 5000ppm. Similarly to the study by Butterworth [Shell Research Ltd., 1982a], a NOEL or NOAEL was not established by the authors, but based on the available information and taking a conservative approach, the NOAEL could be established at the dose level of 1000ppm. The study was conducted prior to the development of GLP and OECD guidelines. However, the principles and the procedures were similar in various respects to the OECD test guidelines.

NaC12-15E3S was fed to rats at dietary concentrations of active ingredient of 0, 40, 200, 500, 1000 and 5000ppm in a 90-day oral feeding study [Shell Research Ltd., 1982a]. During the study, observations were made on the general health and behaviour, body weight and food intake of each rat. At necropsy, major organs were weighed and specified tissues examined histologically. Terminal blood samples were taken for haematological and clinical chemical examinations. All animals survived until their scheduled necropsy date. The general health and behaviour of control and treated rats were similar throughout the study. No significant change was found in female body weights. Male body weights were significantly higher than controls at 500ppm from week 10 onwards and at 200ppm at weeks 11 and 13. At higher concentrations, there was no difference in body weights from the control values. Male and female liver weights significantly increased at 5000ppm. Absolute testes weights were increased at 5000ppm. However, no differences were observed when adjusted for terminal body weight. These increases were not accompanied by histological, clinical chemical or haematological changes and were therefore considered to be adaptive in nature and not a toxic effect of the compound. A NOEL or NOAEL was not indicated by the authors, but based on the available information and taking a conservative approach, the NOAEL is considered to be 1000ppm. It was not indicated in the report whether the study followed the principles of the OECD method 407 and was GLP compliant.

NaC12-14AE2S was tested for systemic toxicity at repeated doses by oral gavage of 0 (group 1), 25 (group 2), 75 (group 3), and 225 (group 4) mg/kg bodyweight [Henkel KGaA, 1994a]. The compound was administered by gavage over a period of 90 days. Ten (10) male and female rats were used for each dose. Five (5) male and female animals of groups 1, 3, and 4 were observed to determine the reversibility of possible compound-related alterations for 28-days after treatment. Four (4) animals died during the treatment period. The mortality of the animals was, however, considered to be incidental. Three (3) animals died due to experimental procedures such as anesthesia for blood sampling and the fourth animal was sacrificed due to a traumatic fracture of the mandibula. No systemic treatment-related effects were observed in any test group. The mean food and water consumption was not affected and the total body weight gain showed no deviations in all male and female test groups. Local treatment effects were only seen in the forestomach. The forestomach of the animals of group 4 showed some lesions such as a hyperplasia, submucosal oedema and chronic ulceration. In groups 2 and 3, 3 out of 10 animals showed small eosinophilic foci in the stratified epithelium of the forestomach. In conclusion, according to the study described, a daily administration of NaC12-14AE2S revealed no systemic toxicity but local treatment-related concentration dependant irritation to differing degrees in the forestomach in all main test groups 2 – 4. Thus, a NOEL-value was not determined. Since there is no human equivalent to the rat forestomach, these effects are not considered to be relevant to human health assessment. Looking at systemic toxicity, behavioural and clinical abnormalities and other general or specific toxic effects, a no adverse effect level (NOAEL) of 225 mg/kg could be established. The study followed the OECD guideline method 408. GLP compliance was not indicated in the study report.

No unusual findings regarding systemic toxicity were noted in a 2-year chronic feeding study in rats in which C12 AE3S was given at 0, 0.1 or 0.5% in the diet for 2 years. An occasional tumour (type and incidence unspecified) was found in various groups. The tumours were characterized as "typical" of those commonly found in aged rats and did not appear to be associated with the ingestion of AES [Tusing et al., 1962 quoted in Arthur D. Little, 1991]. The results of this study suggest that the NOEL for C12AE3S in this 2-year chronic feeding study in rats was greater than 250 mg/kg bw/day. However, the information available is only very limited and thus only a low study reliability score can be assigned.

In a 2-year study, rats (20/sex/group) were administered C12AE3S in the drinking water at a concentration of 0.1% [Arthur D. Little, 1991]. At termination, survival, growth, food consumption, body weights, clinical laboratory findings, hematology and urinalyses were all comparable in control and treated animals. The only unusual finding was slight, but consistently higher water consumption by all rats receiving the test compound in their drinking water and a significant difference in the empty cecum to body weight ratio of females. Absolute organ weights were all comparable to controls and no consistent gross or histopathology was found.

Generally, pathological findings for controls and treated rats after 2 years were varied and consisted predominantly of incidental findings attributable to advanced age. Various types of benign and malignant tumours were found in both groups. The incidence and types of tumours observed in the treated group was similar to that of control animals. A NOEL greater than 75 mg/kg bw/day (equals a dose of 0.1% in drinking water) can be estimated on the basis of the available information.

A few more repeated oral toxicity studies on AES or AES containing formulations are published elsewhere [Arthur D. Little, 1991]. Detailed study descriptions for these studies were not available, but taking the summaries into account these studies appear to confirm the data and information presented in this chapter.

2.2.2.2. Inhalation

Long-term inhalation studies on AES are not available.

2.2.2.3. Dermal route

Subchronic percutaneous toxicity studies were conducted on 2 liquid dishwashing detergents containing anionic surfactant C12-14AES (detergent A: 23%; detergent B: 27%), C12-14 alkyl sulphate (detergent A: 5%; detergent B: 0%), C12-14 alkylamine oxide (detergent A: 3%; detergent B: 5%), ethanol (detergent A: 5%; detergent B: 7%) and water (balance). The detergents were administered dermally to the shaved backs of rabbits (10 animals per group; 5 of each sex) at concentrations of 0, 0.5, 1.0, and 2.5% in distilled water for 6 hr/day, 5 days/week for a total of 65 treatments (91 days). The dose selection was based on the local irritation effects observed in a 14-day pilot study conducted with each detergent. No adverse systemic effects were observed by assessment of haematological parameters or by gross or microscopic tissue examination. Transient slight to moderate dermal irritation at the detergent application site was observed with detergent A. Slight to moderate dermal irritation confined to the detergent application site was noted in the detergent B study [Petersen, 1988].

No further studies investigating the toxicity of AES, other than irritation, after repeated exposure via the dermal route were available.

Table 1 - Summary table of the repeated dose toxicity tests with AES

Animal	Route	Duration	Test Material	Estimated NOEL*	Doses	Reference
Rat	Drinking water	2 years	C12AE3S	>75 mg/kg/d** (0.1%)	0.1%	Arthur D. Little, 1991
Rat	Oral feeding	2 years	C12AE3S	250 mg/kg/d*** (0.5%)	0, 0.1, 0.5%	Arthur D. Little, 1991
Rat	Oral gavage	90 days	NaC12-14AE2S	225 mg/kg/day for systemic toxicity; (local effects in forestomach at all doses)	25, 75, 225 mg/kg/day	Henkel KGaA, 1994a

Rat	Oral feeding	90 days	NaC12-15E3S	50 mg/kg/d*** (1000ppm)	40, 200, 500, 1000, 5000ppm	Shell Research Ltd., 1982a
Rat	Oral feeding	90 days	C12-15E3S C12E3S	50 mg/kg/d*** (1000ppm)	40, 200, 500, 1000, 5000 ppm	Walker, 1967
Rabbits	Dermal	90 days	2 hand dish detergents containing AES at levels of 23 and 27%	> 12.5 mg/kg/d	0, 0.5%, 1%, 2.5%	Petersen, 1988
Rat	Oral gavage	28 days	Blend of C14-18S and C12-13E6.5S		30, 100, 300, 1000 mg/kg bw/d	Shell Oil, 1992
Rat	Oral feeding	21 days	NaC12-15E3S	254 mg/kg bw/d (0.188%)	0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1%, 1.5%	Unilever, 1979a
Rat	Oral feeding	21 days	NH4C12-15E3S	232 mg/kg bw/d (0.188%)	0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1%, 1.5%	Unilever, 1979b

Rat	Oral feeding	21 days	NaC12-15E3S cont. alcohol	108 mg/kg bw/d (0.094%)	0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1%, 1.5%	Unilever, 1980a
Rat	Oral feeding	21 days	NH4C13-15E3S	461 mg/kg bw/d (0.375%)	0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1%, 1.5%	Unilever, 1979c
Rat	Oral feeding	21 days	NaC12-14E3S	120 mg/kg bw/d (0.094%)	0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1% 1.5%	Unilever, 1979d
Rat	Oral feeding	21 days	NH4C16-18E4S	468 mg/kg bw/d (0.375%)	0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1%, 1.5%	Unilever, 1980b
Rat	Oral feeding	21 days	NaC12-15E3S	441 mg/kg bw/d (0.375%)	0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1%, 1.5%	Unilever, 1979e

* NOELs were not expressed in the original study reports, but estimated based on the available information

** estimated based on the assumption of a mean adult rat body weight of 0.4kg and a water consumption of 30ml/day [US Environmental Protection Agency, 1978]

*** estimated based on the assumption of a mean adult rat body weight of 0.4kg and a food consumption of 20g per day (1ppm in food equals 0.05 mg/kg/day) [US Environmental Protection Agency, 1978]

Conclusion

The available oral repeated dose toxicity studies provide a coherent picture on the subacute, subchronic and chronic oral toxicity of AES. In 2 chronic toxicity studies investigating carcinogenicity of AES and four subchronic toxicity studies (3 oral studies with AES, 1 dermal study with AES containing dishwashing liquids), no adverse effects, behavioral or clinical abnormalities of AES were observed up to a dose level of 250 mg/kg body weight per day.

In the subchronic oral gavage study, local treatment related effects were observed in the forestomach of the test animals. These effects can be explained by the irritating nature of the test solutions on the epithelium of the forestomach after repeated administration under the conditions of oral gavage. This is considered to be a response secondary to the irritant properties of AES and specific to the administration procedure. A similar response was not observed when the test material was administered via the diet. Administration via oral gavage is not considered to be relevant for humans because this exposure route is an unlikely scenario for human exposure. Also, there is no equivalent in man to the rat forestomach.

In the subchronic oral feeding studies with AES, general health, body weight and food intake remained within normal limits up to the highest tested dose of 250 mg/kg bw/day, but increased organ weights (liver, kidney) were determined in the highest dose group (250 mg/kg bw/day) of the 2 subchronic oral feeding studies. These increases were unaccompanied by histological changes and are considered to be of an adaptive nature rather than a toxic effect of the test article. The dose level of 250 mg/kg/day is considered to represent a NOAEL.

In a series of 21-day oral feeding studies various AES were evaluated for their repeated dose toxicity. The no observed effect levels derived from these toxicity studies ranged from 108 – 460 mg/kg body weight per day. The organ mostly affected in these studies was the liver, expressed by increased liver weight at high doses, hepatic hypertrophy and occasionally changes in biochemical parameters such as increase of enzyme levels in plasma, generally at levels higher than 250 mg/kg bw/day. Significant increases in weight were also observed in other organs (e.g. kidney, heart, brain) in some of these studies, but only at doses higher than LOELs established for above mentioned liver parameters. With regard to this information, it must be noted that care should be taken in the interpretation due to the low number of animals in the dose groups and the limited information available on the studies. It was considered that, in particular, the observations at dose levels below 250 mg/kg bw/day were not adverse in nature. This evaluation takes into account that at approximately the same dose levels, no adverse effects were seen in the above mentioned subchronic and chronic toxicity studies.

From the available repeated toxicity studies, only the 90-day oral gavage study with NaC12-14AE2S and the 90-day oral feeding study were indicated to be in compliance with the OECD method 407 and GLP regulations and should be considered as most reliable [Henkel KGaA, 1994a, Shell Research Ltd., 1982a]. Although none of the other studies fully complied with the

principles of OECD method 407 or indicated compliance with GLP regulations, their results were consistent with the most reliable studies. In particular, the chronic rat drinking water study and the 2nd rat oral feeding study were conducted following principles and procedures similar to those of OECD method 407 and thus, should be regarded as suitable for inclusion in a weight of evidence approach to evaluating the toxicity of AES.

2.2.3. Genetic Toxicity

2.2.3.1. In Vitro

Bacterial tests

Several alcohol ethoxysulphates were assessed for their potential to induce reverse mutations in the presence and absence of a metabolic activation system in an in vitro bacterial system, the so-called Ames test [Hüls AG, 1996; Hüls AG, 1994 ; Henkel KGaA, 1988; Shell Research, 1980b].

Representing the whole range of studies, a recent OECD method 471 and GLP compliant study [Hüls AG, 1996] should be mentioned at this place: In this study, Salmonella typhimurium strains TA98, TA100, TA1535 and TA 1537 were treated with the triisopranolammonium salt of C12-14AE2S in the Ames test plate incorporation assay as well as the preincubation method. Dose levels covering the range of 1 to 5000 μg/plate, in triplicate both with and without the addition of a metabolizing system (Aroclor 1254 induced rat liver S9 mix) were employed. All 4 bacterial strains exhibited mutagenic responses to the appropriate positive control substances. Solvent controls were also tested with each strain and the mean numbers of spontaneous revertants were in an acceptable range. Mutagenic activity of the test compound to any of the tester strains was not observed with and without metabolic activation. It was therefore concluded that under the chosen test conditions, the triisopranolammonium salt of C12-14AE2S is not a bacterial mutagen.

The majority of the studies evaluated the mutagenicity of AES in Salmonella typhimurium strains TA98, TA100, TA1535, TA 1537 and TA 1538. One study [Shell Research, 1980b], however, evaluated the mutagenicity of NaC12-15E3S in presence and absence of a metabolic activation system in the Escherichia coli strains WP2 and WP2uvrA, in addition to the Salmonella typhimurium strains. Also, in these E. coli strains, the tested AES compounds were not mutagenic under the test conditions. In all tested systems, AES were not found to be mutagenic to bacterial systems.

Non bacterial tests

The mutagenic activity of NaC12-15AE3S was further evaluated in a Saccharomyces gene conversion assay [Shell Research, 1980b]. In this study, it was concluded that the addition of NaC12-15AE3S to liquid suspension cultures of Saccharomyces cerevisiae JD1 with or without metabolic activation did not induce a consistent increase in mitotic gene conversion at either gene locus in two replicate experiments.

AES was examined for mutagenic activity by assaying for the induction of trifluorothymidine resistant mutants in L5178Y TK+/- mouse lymphoma cells after in vitro treatment in the absence and presence of S9 metabolic activation [Research Toxicology Centre S.p.A., 1995]. Under the

reported experimental conditions, it was concluded that in the presence and absence of metabolic activation, the test material NaC12-14AE2S did not induce gene mutations in L5178Y TK+/- mouse lymphoma cells. This study was conducted in compliance with OECD method 476 and GLP regulations.

The ability of NaC12-15E3S to induce chromatid and chromosome aberrations was studied in rat liver cells [Shell Research, 1980b]. In slide cultures of rat liver cells exposed to culture medium containing NaC12-15E3S at concentrations of 25, 50 and 100 μg/ml the frequency of chromatid and chromosome aberrations did not differ significantly from that of the controls cultures.

No morphological cell transformations were observed in Syrian golden hamster embryo cells exposed in culture to concentrations up to 50 mg/ml C12-13E2.5S [Inoue et al., 1980].

In an in vitro transformation study with NaC12-15E3S [Shell Research Ltd., 1983b], the transforming activities of NaC12-15E3S and 1,4-dioxane were determined using cultured C3H 10T1/2 mouse embryo fibroblasts as the target cell population. Monolayer cell cultures were incubated for 24 hours in growth medium containing NaC12-15E3S or 1.4-dioxane. Transformation frequencies were assessed by counting the number of actively dividing, darkly stained cell foci per dish, 3 or 4 weeks after test compound treatment. In conclusion, there was no evidence to suggest that either NaC12-15E3S or 1,4-dioxane increased the frequency of 10T1/2 mouse embryo fibroblasts under the experimental conditions described.

2.2.3.2. In Vivo

NaC12-15E3S has been evaluated in an alkaline elution assay [Shell Research Ltd., 1982b]. In this screen which aims to measure DNA single-strand breaks induced in DNA by reaction with electrophiles, NaC12-15E3S did not cause measurable DNA-strand damage when administered to Wistar rats as a single oral dose of 2.5 ml/kg (equals about half of the LD50 of NaC12-15E3S) for an exposure period of 6 hours. Based on this result it was concluded that neither NaC12-15E3S nor its in situ generated metabolites have any effect upon the integrity of rat liver DNA in vivo under the conditions of the test.

In a series of studies with a 55% AES:45% LAS mixture, no significant differences from control values were noted in a dominant lethal study or in vivo or in vitro cytogenicity studies [Arthur D. Little, 1991]. In the dominant lethal assay, male mice were orally administered either 100, 150, or 200 mg/kg subacutely or 500, 750, or 1000 mg/kg acutely of the surfactant mixture. No significant differences from water-dosed controls were observed in the mutagenic index. Similarly, no significant differences in chromosomal anomalies were found in bone marrow cells of male rats given 40, 500, or 1000 mg/kg of the surfactant mixture orally, then killed 18, 24 or 48 hours post-dosing. Likewise, human leukocytes incubated for 18, 24, or 48 hours with 4, 40 or 200 μg/l of the surfactant mixture exhibited no increased incidence of chromosomal anomalies above the water control group.

Another published in vivo study indicated that AES is not clastogenic. Hope [Hope, 1977] reported that the incorporation of C12-15AES into the diet of rats at a maximum tolerated dose (1.13% active ingredient) for 90 days had no effect on the chromosome of rat bone marrow cells.

Conclusion

A structure activity analysis did not reveal any functional groups in the chemical structure of AES that were associated with mutagenic or genotoxic properties. In all available in vitro and in vivo genotoxicity assays, there is no indication of genetic toxicity of AES. Only 2 studies, an Ames test [Hüls AG, 1997f] and a mouse lymphoma assay [Research Toxicology Centre S.p.A., 1995], were conducted according to OECD guideline methodologies and GLP regulations. However, all the other available in vitro and in vivo studies appear to be well documented and conducted. Some of these studies were published in peer-reviewed journals. Based on the presented data, it is therefore concluded that there is no evidence that AES are either mutagenic or genotoxic.

2.2.4. Carcinogenicity

In a 2-year study, rats (20/sex/group) were administered C12AE3S in the drinking water at a concentration of 0.1%. At termination, survival, growth, food consumption, body weights, clinical laboratory findings, haematology and urinalyses were all comparable in control and treated animals. The only unusual findings were slight, but consistently higher water consumption by all rats receiving the test compound in their drinking water and a significant difference in the empty cecum to body weight ratio of females. Absolute organ weights were all comparable to controls and no consistent gross or histopathology was found. Generally, pathological findings for controls and treated rats after two years on test were varied and consisted predominantly of incidental findings attributable to advanced age. Various types of benign and malignant tumors were found in both groups. The frequency of tumours in the treated group was not significantly different from that of control animals [Arthur D. Little, 1991].

No indications of an increased incidence in tumours were noted in a 2-year chronic feeding study in rats in which C12 AE3S was given at 0, 0.1 or 0.5% in the diet for 2 years. An occasional tumour (type and incidence unspecified) was found in various groups. The tumours were characterized as "typical" of those commonly found in aged rats and did not appear to be associated with the ingestion of AES [Tusing et al., 1962 quoted in Arthur D. Little, 1991].

An 5% aqueous solution of C12E3S (0.1ml) was applied twice weekly on the skin of 30 female Swiss mice [Tusing et al., 1962 quoted in Arthur D. Little, 1991]. No papillomas or other tumours were found under these exposure conditions.

In its report to the Soap and Detergent industry [Arthur D. Little, 1991], Arthur D. Little reported on a study in which an aqueous solution of 18.5% C16-18AES and 15.6% LAS was applied 3 times a week on the skin of Swiss ICR mice for 18 months. Under these conditions, the test solutions did not induce any carcinogenic response either on the skin or systemically.

Conclusion

The available oral and dermal long term toxicity/carcinogenicity studies, even if not performed according to accepted guidelines for carcinogenicity bioassays, appear to be conducted and

documented in an acceptable manner. It is therefore concluded that there is sufficient evidence that AES is not carcinogenic in the tested species under the conditions described.

2.2.5. Reproductive toxicity

As part of a chronic feeding study, 10 rats/sex/group fed diets containing 0.1% of C12AES were mated after 14 weeks on the test [Arthur D. Little, 1991]. The F1 generation was maintained on the parental diet and mated at 100 days of age. The F2 generation was fed the same diet for 5 weeks, and then killed. No adverse effects on fertility, lactation, litter size or survival and growth of the offspring were seen. Haematological, biochemical and histopathological findings were comparable to controls. From this study it can be concluded that the NOEL for reproductive toxicity is estimated to be greater than 50 mg/kg bw/day. This estimation was based on the assumption of a mean adult rat body weight of 0.4kg and a water consumption of 30 ml/day [US Environmental Protection Agency, 1978].

No adverse parental toxicity or significant differences in either litter parameters or viability of offspring were noted in two generations of rats fed diets containing either 0.1% C12AES [Tusing et al., 1962] or 1% (reported to equal an exposure of 800 mg/kg/day) of a detergent formulation containing 55%TE3S and 45% LAS [Nolen, et al., 1975].

In available subchronic [Henkel KGaA, 1994a, Shell Research Ltd., 1982a, Walker, 1967] and chronic toxicity studies [Arthur D. Little, 1991, Hüls AG, 1997b] on various AES (NaC12-14AE2S, CaC123-15AE3S, C12AE3S), the primary sex organs of the males and females did not show evidence for treatment-related adverse effects as indicated by organ weight differences, gross examination, and microscopic histology examination at the highest tested exposure levels of 250 mg/kg bw/day.

Further information can be deduced from a two-generation reproduction study with NaC12-14AE2S [Henkel 1999]. This GLP-study followed the OECD guideline method 416. Four groups of thirty male and thirty female Sprague Dawley rats (strain Crl:CD(SD)BR) (F0 generation) were dosed via the drinking water. Concentrations used were 0 (control), 0.03, 0.1 and 0.3 %, which corresponded to daily doses of ca. 0, 30, 100 and 300 mg/kg/day.

There were some changes indicative of parental toxicity in the group treated with 0.3 % of the test substance, which were characterised by reduced straight line velocity of the sperm. The observed reduced triglyceride levels (female) and increased percentage neutrophil counts (males) were slight and within the range of the historical control data. There was evidence of toxicity on pup development at this dose level that was characterised by an increase in the time taken for sexual development of the male (not significant) and female (significant) offspring. No other developmental parameters were affected.

There were some changes seen in reduced straight line velocity of the sperm, reduced trigylceride levels (female) and increased percentage neutrophil counts (males) in the group treated at 0.1 %. All the changes were either not statistically significant or within the range of the historical control data. There was no evidence of toxicity on pup development.

There was no evidence of toxicity on pup development in the group treated with 0.03 %.

Decreased liver weights of the F0 and F1 male dose groups were observed which was not confirmed in the F2 generation dose group.

The male F0 generation showed a small but significant reduction in bodyweight-liver weight ratios, but the corresponding brain related liver weights and the absolute liver weights developed not in a dose dependant way. For the F1 generation where similar results were reported, no dose-response relationship was detected either. No influence on liver weight development was seen in the F2 generation. None of the groups revealed any histopathological or clinical-chemical findings, which could be attributed to hepatotoxicity. This led to the conclusion that this untypical liver weight reduction was of no toxicological relevance, additionally underlined by the absence of such effects in the studies for subchronic toxicity mentioned above.

In summary, there was no effect of treatment at any dose level on reproduction of the parents or offspring (NOAEL > 3 %; > 300 mg/kg/day)

Based on this study an overall NOAEL for systemic effects of 0.1 % (86.6 mg/kg bw) for the F0 generation and a NOAEL of 0.1 % (149.5 mg/kg bw) for the F1 generation can be deduced.

Conclusion

Alcohol ethoxysulphates were evaluated for reproductive effects in rats. The key study (Henkel, 1999) fulfilled OECD guideline protocols and was conducted according to GLP standards. No information on the guidelines and GLP was available for another reproduction study that was cited in the scientific literature [Arthur D. Little, 1991]. AES did not adversely affect reproduction in the rat and the NOAEL for reproductive effects was > 300 mg/kg; slight systemic effects were observed in the parental and F1 generation with a NOAEL of 86 and 149 mg/kg, respectively.

2.2.6. Developmental Toxicity /Teratogenicity

2.2.6.1. Oral route

NaC12-14AE2S was tested in a segment II embryotoxicity study [Henkel KGaA, 1994b]. The purpose of the study was to assess the effects of orally administered NaC12-14AE2S on embryonic and foetal development in pregnant CD-rats. The study followed the guidelines of OECD method 414 "Teratogenicity" and complied with the OECD principles of GLP. In this study, NaC12-14AE2S was administered orally by gavage at dose levels of 0, 100, 300, and 1000 mg/kg body weight once daily from day 6 to day 15 of gestation. Each group consisted of at least 24 female rats. A standard dose volume of 10 ml/kg body weight was used and the control animals were dosed with the vehicle alone over the period described. Clinical condition and reaction to treatment were recorded at least once daily. Body weights were reported for days 0, 6, 16 and 20 of gestation. All surviving females were sacrificed on day 20 of gestation and the foetuses were removed by caesarean section. At necropsy the females were examined macroscopically and live foetuses were weighed, sexed and examined for visceral and skeletal

abnormalities. In summary, the results of the study showed that repeated oral administration (day 6 – day 15 post coitum) of NaC12-14AE2S to pregnant rats did not cause symptoms of cumulative toxicity up to a dose level of 1000 mg/kg/day. No compound-related symptoms were observed and no treatment-related abnormalities were found at necropsy of the females. All females had viable foetuses. Pre-implantation loss, post-implementation loss, mean number of resorptions, embryonic deaths, total foetuses, mean foetal placental and uterus weights were not affected by the treatment. Foetal sex ratio was comparable in all groups. There were no treatment-related foetal abnormalities at necropsy and no treatment-related effects in the reproduction data. In conclusion, in the described embryotoxicity study, NaC12-14AE2S was not cumulatively toxic to pregnant rats and did not reveal any teratogenic potential at the tested dose levels. Thus, based on the available information, the NOAEL for teratogenicity and developmental toxicity are assessed to be greater than 1000 mg/kg bw/day.

NaC12-15AE3S was administered orally by gavage to pregnant Colworth-Wistar rats at dose levels of 0, 375 and 750 mg/kg/day once daily from day 6 to 15 of gestation [Unilever, 1980c]. Two different samples of the test material were tested. Fifteen (15) animals were used per dose group, 10 for dissection and 5 for natural parturition. Throughout the study, the females were monitored for signs of toxicity. Upon necropsy, fetal toxicity was determined by evaluating pre-implantation and post-implantation fetal loss and fetal weight. Fetuses were evaluated for externally visible malformations, as well as malformations of the internal organs and skeleton. In the post-partum phase pup mortalities, body weights and litter size as well as incidence of external and gross visceral and skeletal defects were monitored until weaning day 21. The resulting data were compared to the control group. In summary, NaC12-15AE3S induced maternal toxicity, indicated by body weight changes and other clinical and behavioural observations, when administered by gavage to pregnant rats at doses of 750 mg/kg. The authors were unable to detect any specific abnormality which would indicate a developmental toxicity or teratogenic response related to the treatment. This study was not conducted according to any recognized guideline. However, the study was conducted according to GLP, is well-documented and judged to be scientifically acceptable. Based on the available information the NOAEL for maternal toxicity was estimated to be 375 mg/kg bw/day and the NOAEL for teratogenic effects or developmental toxicity is greater than 750 mg/kg bw/day.

NH4C13-15AE3S was administered orally by gavage to pregnant Colworth-Wistar rats at dose levels of 0, 63, 125, 250 and 500 mg/kg/day once daily from day 6 to 15 of gestation [Unilever, 1986a]. Fifteen (15) animals were used per dose group, 10 for dissection and 5 for natural parturition. No detailed information was available on the study design. Some slight maternal toxicity indicated by body weight changes and other clinical observations (e.g. diarrhoea, respiratory wheeziness) was seen in rats with exposure to 250 and 500 mg/kg bw/day, but given the limited information available, there is some uncertainty regarding the severity of these effects. No evidence of developmental toxicity or a teratogenic response to the treatment were reported at any dose level. This study was not conducted according to GLP or according to any recognized guideline. Given the lack of information and the uncertainty mentioned before, a NOAEL could not be reliably determined.

NaC12-14AE3S was administered orally by gavage to pregnant Colworth-Wistar rats at dose levels of 0, 93, 187, 375 and 750 mg/kg/day once daily from day 6 to 15 of gestation [Unilever,

1986b]. Fifteen (15) animals were used per dose group, 10 for dissection and 5 for natural parturition. Maternal and foetus effects were evaluated as described previously (i.e study with NaC12-15AE3S). The treatment of pregnant rats with NaC12-14AE3S during days 6-15 of gestation did induce some maternal toxicity at the dose level of 750 mg/kg bw/day. No evidence of treatment-related teratogenic effects or developmental toxicity was reported. This study was not conducted according to GLP or according to any recognized guideline. However, the study appeared well-conducted, was well-documented and judged to be scientifically acceptable. Based on the available information the NOAEL for maternal toxicity was determined to be 375 mg/kg bw/day and the NOAEL for teratogenic or developmental effects is estimated to be greater than 750 mg/kg bw/day.

NaC16-18AE4S was administered orally by gavage to pregnant Colworth-Wistar rats at dose levels of 0, 63, 125, 250 and 500 mg/kg/day once daily from day 6 to 15 of gestation [Unilever, 1986c]. Twenty (20) animals were used per dose group, 15 for dissection and 5 for natural parturition. Forty (40) animals were used for the negative control. Maternal, foetus and post-partum effects were evaluated as described previously (i.e study with NaC12-15AE3S). In summary, there was no evidence of teratogenic potential or developmental toxicity. This study was not conducted according to any recognized guideline. The study was conducted according to GLP, is well-documented and judged to be scientifically acceptable. Based on the available information, the NOAEL for both maternal toxicity, teratogenic and developmental effects appeared to be greater than 500 mg/kg bw/day.

In a last study of this series, NaC12-15E3S was administered orally by gavage to pregnant Colworth-Wistar rats at dose levels of 0, 125, 250, 500 and 1000 mg/kg/day once daily from day 6 to 15 of gestation [Unilever, 1979f]. Fifteen (15) animals were used per dose group, 10 for dissection and 5 for natural parturition. Maternal, foetus and post-partum effects were evaluated as described previously. The authors of the study concluded that a degree of maternal toxicity indicated by a significant reduction in body weight gain of NaC12-15E3S was observed at the highest dose level of 1000 mg/kg. However, no evidence of treatment-related developmental toxicity or teratogenic effects was detected. This study was not conducted in compliance with GLP or according to any recognized guideline. The study appeared well-conducted, was well-documented and judged to be scientifically acceptable.

Pregnant rats were administered 50, 100, and 500 mg/kg/day of C12-13AES by oral gavage on days 6-15 of gestation. Effects observed were a decrease in maternal body weight gain and food consumption [Arthur D. Little, 1991]. There were no treatment-related maternal effects noted at necropsy or following a uterine examination on day 13 of gestation. The incidence of foetal malformations in AES-treated groups was not different from the control group.

Several investigators have studied the effects of administering a commercial liquid detergent formulation containing both AES and LAS to pregnant mice, rats and rabbits [Iseki, 1972; Nolen, et al., 1975; Palmer, et al., 1975]. Except at dosage levels which were toxic to the dams, no significant differences in the litter parameters of laboratory animals compared to control values were noted in these studies. Levels up to 300 mg/kg of a mixture containing 55% TE3S and 45% LAS given orally to rabbits on days 2-16 of gestation up to 800 mg/kg given to rats on days 6-15 of gestation gave no indications of any embryotoxic or teratogenic effects attributable

to AES [Nolen, et al., 1975]. In these exploratory investigations, there were no indications that detergent formulations containing AES at doses which are several orders of magnitude above possible human exposure levels posed any teratogenic hazard to laboratory animals.

2.2.6.2. Dermal route

There are no studies available that examined the teratogenicity and developmental toxicity of AES after dermal exposure.

Conclusion

Alcohol ethoxysulphates were evaluated for teratogenic or embryotoxic effects mainly in rats, but in a few investigations also in mice and rabbits. Although the majority of these studies did not fulfill all requirements of existing guideline protocols and were not conducted according to GLP standards, the studies appeared to be well conducted and documented. Noteworthy is the segment II embryotoxicity study [Henkel KGaA, 1994b] which followed OECD guidelines and complied with the OECD principles of GLP. In this study which which was rated to be reliable without limitations according to the Klimisch criteria [Klimisch et al., 1997], AES showed no cumulative toxicity in pregnant rats and did not reveal any embryotoxic or teratogenic potential at the highest tested dose levels of 1000 mg/kg body weight.

The absence of a teratogenic potential and developmental toxicity of AES was confirmed in a series of teratology screening studies [Unilever, 1979f]. Although there were limitations in the design of the study, in particular with regard to the size of the dose groups and the absence of some clinical/biochemical parameters, the overall quality of these studies is judged to be appropriate and scientifically valid.

Based on the presented information, it is concluded that there is sufficient evidence that AES is not teratogenic or a developmental toxicant under the conditions described. A NOAEL greater than 1000 mg/kg bw/day can be estimated for teratogenicity and embryotoxicity on the basis of the segment II embryotoxicity study which is judged to be of highest reliability. The NOAEL for developmental toxicity appears to be greater than 750 mg/kg bw/day.

2.2.7. Biokinetics

McDermott et al. (1975) studied the absorption of C16AE3S and C16AE9S, labelled with ^{14}C in the 1-position of the alkyl chain, after oral exposure in man and rats. Seventy-two hours after administration of C16AE3S, radioactive material was mainly excreted via urine (man: 80%; rat: 50%) and to a lesser extent via faeces (man: 9%; rat: 26%) and air (man: 7%; rat: 12%). For C16AE9S however, the radioactivity was mainly excreted via faeces (man: 75%; rat: 82%) and to a lesser extend via urine (man: 4%; rat: 0.6%) and air (man: 6%; rat: 4%). The length of the ethoxylate portion of an AES molecule appears to determine the metabolic fate of the compound following oral administration in both man and rat. There was no evidence of hydrolysis of the sulphate group or of metabolism of the ethoxylate portion of the molecule. The major metabolite found in urine had the following structure: -OOCCH2(OCH2CH2)xOSO3$^-$ where x equals either 3 or 9, respectively [McDermott et al., 1975].

In a similar investigation, Taylor et al. (1978) studied the metabolic fate of orally, intraperitoneally or intravenously administered ^{14}C-C11AE3S and ^{14}C-C12AE3S in the rat. The authors observed that both compounds were extensively metabolized (ω, β oxidation) with the proportion of radioactivity appearing in urine and respired air generally independent of the route of administration. Some sex differences in the proportions of radioactivity excreted in urine and respired air was seen, but total recoveries for both compounds were comparable. By the oral route, 67% of the administered radioactivity with C11AE3S appeared in the urine of male rats compared to 45% in females; expired air contained 19% and 35% of administered radioactivity respectively; 4-5% was present in faeces for both sexes. The major urinary metabolite of C12AE3S was identified as 2-(triethoxy sulphate) acetic acid, with C11AE3S, the major urinary metabolite was tentatively identified as 3-(triethoxysulfate) propionic acid.

Taylor et al. (1978) measured the percutaneous absorption of ^{14}C-labelled NaC12AE3S. The NaC12AE3S was applied to rats as 150 μl of a 1% v/v solution. The ^{14}C-levels were measured in urine collected over 48 hours. Penetration of NaC12AE3S was 0.39 +/- 0.12 $\mu g/cm^2$. In experiments in which application was continued for up to 20 minutes, skin penetration was proportional to the duration of the contact. It was also proportional to the number of applications.

Conclusion

Following oral exposure, AES is readily absorbed in the gastrointestinal tract in man and rat and excreted principally via the urine. The length of the ethoxylate portion in an AES molecule seems to have an important impact on the biokinetics of AES in humans and in the rat. Alcohol ethoxysulphates with longer ethoxylate chains (>7-9 EO units) are excreted at a higher proportion in the faeces. Once absorbed, AES is extensively metabolized by beta- or omega oxidation.

The dermal absorption of AES is relatively poor as can be expected from an ionic molecule. The percutaneous absorption of C12AE3S was measured in a rat in vivo study. The study determined a dermal flux of the tested compound of 0.0163 $\mu g/cm^2/h$.

2.2.8. Experience from human exposure

Allergic contact sensitisation:
Over the years very many formulations containing a variety of AES concentrations are reported to have been tested in Human Repeat Insult Patch tests (HRIPT) failing to show evidence of contact sensitisation (see, e.g., [Nusair TL et al., 1988]). Available detailed examples include two HRIPTs reported as follows:

In one test [Procter & Gamble, 1998], 102 volunteers were treated with patches of a 0.05% (w/v) aqueous solution of a detergent formulation containing 37% AES (Na AE1.4S, CAS# 68585-34-2). The patches were applied on the upper arms, under fully occlusive conditions. Test material was applied for 24 hours, 3 times a week, for 3 weeks during the induction period. After a 14-17-day rest, a 24-hour challenge patch was applied on the original and alternate arm sites. There was no evidence of skin sensitisation in any of the 102 subjects who completed the test.

In another test [Procter & Gamble, 1994], 87 volunteers were treated with patches of a 0.2% (w/v) aqueous solution of a formulation containing 6% AES (Na AE3S, CAS# 68585-34-2). The patches were applied on the upper arms, under fully occlusive conditions. Test material was applied for 24 hours, 3 times a week at the same skin site, for 3 weeks during the induction period. After a 14-17-day rest, a 24-hour challenge patch was applied on the original and alternate arm sites. There was no evidence of skin sensitisation in any of the 87 subjects who completed the test.

Skin irritation

The cumulative skin irritation effects of formulations containing AES have been investigated in six separate "24-hour Repeat Application Patch Test" studies [Procter & Gamble, 2000a]; [Procter & Gamble, 2001]; [Procter & Gamble, 2000b]; [Procter & Gamble, 2000c] [Procter & Gamble, 2000d], [Procter & Gamble, 2000e]. In each study 12 volunteers were treated with patches of a 0.1% (w/v) aqueous solution of detergent formulations containing AES (Na AES CAS# 68585-34-2). The patches were applied on the upper arms, under fully occlusive conditions. Test material was applied for 24 hours, 3 times a week at the same skin site, for a total of one week. After the end of each 24 hour application period, the skin was graded for irritation according to a 0 – 4 scoring scale. A total of 12 different detergent formulations were tested with the following AES concentrations (% w/v): 11, 13, 16, 18, 19, 20. A total of 72 volunteers were tested. All the formulations tested resulted in cumulative average skin irritation scores lower than 0.8 (they ranged between 0.05 and 0.79), which corresponds to a very mild effect.

In a separate, similar study the cumulative irritancy potential of a detergent formulation containing 11.4% (w/v) AES (Na AES CAS# 68891-38-3) was investigated under open (non-occlusive) conditions [Procter & Gamble, 2001]. A total of 12 volunteers were treated with 0.3 ml of undiluted, 30% (w/v), and 10% (w/v) aqueous dilutions of the detergent formulation, which were applied on an open application patch on the upper arms. Test materials were applied for 24 hours, 3 times a week at the same skin site, for a total of one week. After the end of each 24 hour application period, the skin was graded for irritation according to a 0 – 4 scoring scale. The cumulative average scores for the undiluted, 30%, and 10% detergent formulation were 0.26, 0.03, and 0.03, respectively. These score are all indicative of a very mild effect.

Conclusion

The human experience data supports the lack of allergic contact sensitisation potential of formulations containing AES. The skin irritation potential of aqueous solutions of detergent product formulations under conditions simulating relevant consumer use can be expected to be mild after repeated contact with human skin.

2.2.9. Identification of critical endpoints

2.2.9.1. Overview on hazard identification

Alcohol ethoxysulphates are considered to be of low toxicity after acute oral and dermal exposure. The estimated LD50 is higher than 2000 mg/kg body weight. Reliable data on acute inhalation are not available, but given the irritant nature of AES, it is expected that a high AES aerosol concentration may be irritating to the respiratory tract. However, inhalation is not viewed as a significant route of exposure. AES is mainly used in liquid media and due to its very low vapour pressure, exposure is unlikely to occur. The only possible exposure could be due to the use of powdered formulations or the use of AES in spray cleaner formulations.

The skin and eye irritation potential is concentration dependent. AES concentrations higher than 70% are moderately to severely irritating to rabbit skin under the conditions of 4-hour semi-occluded patch tests and moderately to severely irritating to rabbit eyes. Formulations containing more than 20% AES are classified as skin and eye irritants unless data are available that show absence of irritation potential as defined by the EC criteria. At concentrations below 1%, AES are considered as virtually non-irritating.

AES are not considered to be skin sensitizers. A substantial amount of skin sensitization studies in guinea pigs following either the Magnusson-Kligman maximization or the Buehler testing protocol demonstrate the absence of skin sensitization potential and only very few studies indicated a weak sensitization potential of individual AES. Human experience further supports the assessment that AES are not sensitizing.

The available oral and dermal repeated dose toxicity studies provide a coherent picture on the subacute, subchronic and chronic toxicity of AES. In 2 chronic and four subchronic toxicity studies (3 oral studies with AES, 1 dermal study with AES containing dishwashing liquids), no systemic adverse effects of AES were observed up to the highest tested dose levels of 250 mg/kg bw/day. In 2 subchronic oral feeding studies a slight, but significant increase in organ weights (liver in males and females in both studies, male kidney in one study) was observed at the dose of 250 mg/kg bw/day, but these increases were not accompanied by histological changes and were therefore considered to be adaptive in nature and not a toxic effect of the AES. In two out of seven 21-day oral feeding studies, hepatic hypertrophy and slight increases in plasma enzyme levels were observed at doses of about 120 mg/kg/d. However, in the other 5 21-day oral feeding studies the estimated NOELs ranged from 232 – 468 mg/kg/d. Only little information was available on these 21-days studies, but similarly to above mentioned subchronic and chronic oral toxicity studies, the effects seen in the liver are not considered to be of adverse nature.

AES are not considered to be mutagenic, genotoxic or carcinogenic. Although most studies addressing these endpoints were not performed according to accepted guidelines, the picture is very coherent. In all the in vitro and in vivo assays there was no indication of genetic toxicity of AES. Long-term carcinogenicity studies did not indicate any potential of AES to induce tumours.

Substantial information is available on teratogenicity, embryotoxicity and toxicity to reproduction of AES. Taken all together, it can be concluded that AES is not cumulatively toxic to pregnant rats and did not reveal teratogenic, developmental reproductive effects at the highest tested dose levels of >300 mg/kg body weight per day.

2.2.9.2 Rationale for identification of critical endpoints

Dermal exposure is the main exposure route for consumers and subsequently, dermal effects such as skin irritation and sensitization as well as long-term dermal toxicity have to be considered with regard to the human risk assessment. A substantial amount of data is available addressing the skin irritation and skin sensitization potential of AES solutions and AES containing consumer product formulations. Dermal penetration studies in rats have shown that AES has the potential to penetrate the skin and become systemically available. There are only a few dermal studies available, but by using bridging assumptions, systemic effects after dermal exposure can also be assessed using the results of oral repeated dose toxicity studies in experimental animals.

2.2.9.3 Adverse effects related to accidental exposure

The acute oral and dermal LD50 of solutions containing AES at concentrations up to 70% is greater than 2000 mg/kg. This level of toxicity is generally considered as low. AES is present in detergent formulations at 28% as a maximum. Generally, accidental oral exposure to a surfactant containing formulation such as detergents poses a minor risk of aspiration.

The available information suggest that concentrated solutions containing AES at concentrations above 20-30% may be moderately to severely irritating to eyes and slightly to moderately irritating to skin. Thus, eye and prolonged skin contact with neat products should be avoided. Other surfactants present in the formulation could contribute to these effects. It has, however, been observed that the overall irritation profile of AES containing detergent and cleaning formulations is not necessarily additive and is less than expected based on the individual components. Nevertheless, in case of accidental eye contact, immediate rinsing with plenty of water is recommended. This immediate action has been shown in animal experiments to minimize irritation effects.

2.2.10. Determination of NOAEL or quantitative evaluation of data

As discussed before, the available oral and dermal repeated dose toxicity studies provide a coherent picture and demonstrate low toxicity of AES.

In the available chronic and subchronic toxicity studies, no effects were seen at levels up to 75 mg/kg bw/day and no adverse effects of AES were observed up to the highest tested dose levels of 250 mg/kg bw/day. In 2 subchronic oral feeding studies a slight, but significant increase of organ weights (e.g. liver) was observed at the dose of 250 mg/kg bw/day. These increases were not accompanied by histological changes and were therefore considered to be an adaptation to the test material and not a toxic effect of the AES. In a subchronic oral gavage study in rats, local treatment effects were observed in the test animals. These effects can be explained by the irritating nature of the test solutions on the epithelium of the forestomach under the test conditions. These types of effects are not considered to be relevant for humans because they are a concentration-dependent response to a direct irritation and also the fact that the exposure scenario reflected in the oral gavage study is not of relevance to human exposure scenarios occurring in real life. There is also no equivalent to the rat forestomach in man. Following this rationale, a NOAEL of 250 mg/kg bw/day could be established. With regard to teratogenicity of

AES, a NOAEL greater than 1000 mg/kg bw/day is suggested. At this exposure level, no evidence for teratogenicity was found in a reliable segment II embryotoxicity study. In a series of teratology screening studies which monitored pup development up to weaning day 21 no developmental effects were observed for AES at the highest exposure level of 750 mg/kg/day.

However, it is recognized that there might be a different view with regard to the interpretation of the data and the establishment of a NOEL (or NOAEL) for systemic toxicity of AES. Alternatively to the discussion above, there might be the conservative view that the increase in the liver weight accompanied by the increase of certain enzymes in the plasma in one of the subchronic oral feeding studies is indicative of an (adverse) effect.

For assessing the risk associated with human exposure to AES in context of its use in laundry and cleaning products, it is therefore suggested to take a conservative approach by using a no observed effect level (NOEL) of 75 mg/kg bw/day. This value was derived from the results of a 2-year drinking water study in rats.

3 Effects

3.1 Aquatic toxicity

3.1.1 Acute data

Acute toxicity data are available in several review articles (ADL 1991; BKH 1994; Madsen 2000). As a large chronic data base exists (Section 6.1.2) the acute data have not been further considered for the HERA risk assessment.

3.1.2 Chronic data

The following chronic toxicity data are available in reviews or have been identified during this HERA assessment project.

Table 2 Chronic toxicity data

Fish and other aquatic vertebrates

C#		EO#		Linearity	Species	Endpoint	Exposure	Value (mg/l)	Ref
Avg	Distn	Avg	Distn						
12		0		?	Saccobranchus fossilis	60 d	Semi-static	>2.24	Dalela et al, 1981
?	12-13	1	?	?	P. promelas	30 d NOEC	?	0.88	BKH 1994
?	12-14	2	?	?	O. mykiss	28 d growth	flow-through	0.1	Scholz 1997
?	12-15	3	?	?	O. mykiss	28 d NOEC	flow-through Measured	0.12	BUA 1997
13.7	?	2.25	?	?	P. promelas	365 d NOEC	Measured	0.1	Maki 1979
?	14-15	2.25	?	?	P. promelas (juvenile)	45 d LC50	? (flow-through)	0.44	ADL 1991
?	14-15	2.25	?	?	P. promelas (fry)	45 d LC50	? (flow-through)	0.63	ADL 1991
?	14-15	2.25	?	?	P. promelas	45 d LC50	? (flow-through)	0.94	ADL 1991
?	14-16	2.25	?	?	P. promelas	45 d LC50	?	0.1	BKH 1994
17.3	16-18	0			Brachydanio rerio	OECD 204, NOEC		1.7	Steber et al 1988
17	?	3	?	?	P. promelas	365 d NOEC	?	0.13	BKH 1994

Invertebrates

C#		EO#		Linearity	Species	Endpoint	Exposure	Value (mg/l)	Ref
Avg	Distn	Avg	Distn						
12	99%	0	-	-	C. dubia	7 d NOEC	Flow-through	0.88	Dyer et al 1997
12	>95% Pure	1	>95% Pure	?	C. dubia	7 d NOEC	Flow-through	0.34	Dyer et al 2000
12	>95% Pure	2	>95% Pure	?	C. dubia	7 d NOEC	Flow-through	6.3	Dyer et al 2000
12	100% Pure	2	100% Pure	?	Brachionus calyciflorus	2 d EC20	Measured	0.97-1.1	Versteeg et al, 1997
12	>95% Pure	4	>95% Pure	?	C. dubia	7 d NOEC	Flow-through	2.7	Dyer et al 2000
12	99% pure	4	99% pure	?	B. calyciflorus	2 d EC20	Measured	2.3	Versteeg et al 1997
12	>90% Pure	8	>90% Pure	?	C. dubia	7 d NOEC	Flow-through	1.2	Dyer et al 2000
?	12-14	2	?	?	D. magna	21 d repro	Semi-static Nominal	0.72	Scholz 1997
?	12-14	>2	?	?	D. magna	21 d NOEC	Semi-static	0.7	BKH 1994
?	12-15	3	?	?	D. magna	21 d repro	Semi-static Measured	0.34	BUA 1997
13	>95% Pure	2	>95% Pure	?	C. dubia	7 d NOEC	Flow-through	0.28	Dyer et al 2000
13	100% pure	2	100% pure	?	B. calyciflorus	2 d EC20	Measured	0.49	Versteeg et al 1997
13.67	13-15	2.25	?	?	D. magna	21 d NOEC	Measured	0.27	Maki 1979
14	>95%	0	-	-	C. dubia	7 d NOEC	Flow-through	0.<0.062	Dyer et al 1997
14	>95% Pure	1	>95% Pure	?	C. dubia	7 d NOEC	Flow-through	0.34	Dyer et al 2000
14	>95% Pure	2	>95% Pure	?	C. dubia	7 d NOEC	Flow-through	0.31	Dyer et al 2000
14	100% pure	2	100% pure	?	B. calyciflorus	2 d EC20	Measured	0.13	Versteeg et al 1997
14	>95% Pure	4	>95% Pure	?	C. dubia	7 d NOEC	Flow-through	1.1	Dyer et al 2000
14	98% pure	4	98% pure	?	B. calyciflorus	2 d EC20	Measured	0.37	Versteeg et al 1997

?	14-15	0			C. dubia	7 d NOEC	Flow-through	0.081	Dyer et al 1997
?	14-15	2.25	?	?	D. magna	21 d NOEC	Nominal	0.18	BKH 1994
?	14-16	2.25	?	?	D. magna	21 d NOEC	?	0.27	BKH 1994
15	>95%	0	-	-	C. dubia	7 d NOEC	Flow-through	0.23	Dyer et al 1997
15	>95% Pure	1	>95 % Pure	?	C. dubia	7 d NOEC	Flow-through	0.08	Dyer et al 2000
15	>95% Pure	2	>95 % Pure	?	C. dubia	7 d NOEC	Flow-through	0.06	Dyer et al 2000
15	>95% Pure	4	>95 % Pure	?	C. dubia	7 d NOEC	Flow-through	0.15	Dyer et al 2000
15	99% pure	4	99% pure	?	B. calyciflorus	2 d EC20	Measured	0.22	Versteeg et al 1997
15	>90% Pure	8	>90 % Pure	?	C. dubia	7 d NOEC	Flow-through	5.8	Dyer et al 2000
16	>95% pure	0	-	-	C. dubia	7 d NOEC	Flow-through	0.20	Dyer et al 1997
17.3	16-18	0			D. magna	21 d NOEC		16.5	Steber et al 1988
18	>95% pure	0	-	-	C. dubia	7 d NOEC	Flow-through	0.60	Dyer et al 2000

Algae

C#		EO#		Linearity	Species	Endpoint	Exposure	Value	Ref
Avg	Distn	Avg	Distn						
12		0			S. capricornutum	96 h NOEC Growth inhibition		12	Nyholm & Damgaard, 1990
12		?			River water 'community'	Chlorophy 1 a NOEC	3 weeks	70 mg/l (enhancement at 5 mg/l)	Drewa 1989
?	12-13	?	?	?	Selenastrum capricornutum	?	5 d NOEC	50.5	BKH 1994
?	12-14	2	?	?	Scenedesmus subspicatus	72 h NOEC AUGC	Static Nominal	0.72	Scholz 1997
?	12-14	2	?	?	Scenedesmus subspicatus	96 h NOEC	Static Nominal	0.35	BKH 1994
?	12-15	3	?	?	Scenedesmus subspicatus	72 h NOEC	Static Measured	0.9	BUA 1997
?	14-15	?	?	?	Selenastrum capricornutum	NOEC Test duration unknown	?	21	BKH 1994
17.3	16-18	0			Scenedesmus subspicatus	72 h NOEC	Static	17	Henkel 1996

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Annex 1 CAS # covered in family

CAS Number	CAS Description
27028-82-6	Ethanol, 2,2',2"-nitrilotris-, compd. with a-sulfo-w-(dodecyloxy)poly(oxy-1,2-ethanediyl) (1:1)
54116-08-4	Poly(oxy-1,2-ethanediyl), a-sulfo-w-tridecyloxy)-, sodium salt
67762-19-0	Poly(oxy-1,2-ethanediyl), a-sulfo-w-hydroxy-, C10-16-alkyl ethers, ammonium salts
68037-05-8	Poly(oxy-1,2-ethanediyl), a-sulfo-w-hydroxy-, C6-10-alkyl ethers, ammonium salts
68037-06-9	Poly(oxy-1,2-ethanediyl), a-sulfo-w-hydroxy-, C6-10-alkyl ethers
68540-47-6	Ethanol, 2,2',2"-nitrilotris-, compd. with a-sulfo-w-(tetradecyloxy)poly(oxy-1,2-ethanediyl) (1:1)
68585-34-2	Poly(oxy-1,2-ethanediyl), a-sulfo-w-hydroxy-, C10-16-alkyl ethers, sodium salts
68585-40-0	Poly(oxy-1,2-ethanediyl), a-sulfo-w-hydroxy-, C16-18-alkyl ethers, sodium salts
68891-38-3	Poly(oxy-1,2-ethanediyl), a-sulfo-w-hydroxy-, C12-14-alkyl ethers, sodium salts
96130-61-9	Poly(oxy-1,2-ethanediyl), a-sulfo-w-hydroxy-, C9-11-alkyl ethers, sodium salts
105859-96-9	Ethanol, 2,2',2"-nitrilotris-, compds. with polyethylene glycol hydrogen sulfate C11-15-sec-alkyl ether ammonium salts
125301-92-0	Poly(oxy-1,2-ethanediyl), a-sulfo-w-hydroxy-, C12-15-alkyl ethers, sodium salts
125304-06-5	Ethanol, 2,2',2"-nitrilotris-, compds. with polyethylene glycol hydrogen sulfate C16-18-alkyl ether
129783-23-9	Ethanol, 2,2'-iminobis-, compds. with polyethylene glycol hydrogen sulfate C12-15-alkyl ethers
157627-92-4	Alcohols, C10-16, ethoxylated, sulfates, mono(hydroxyethyl)ammonium salts (>1 <2.5 mol EO)
157707-82-9	Alcohols, C14-16, ethoxylated, sulfates, sodium salts (>1 <2.5 mol EO)
162201-45-8	Ethanol, 2-amino-, compds. with polyethylene glycol hydrogen sulfate C12-15-alkyl ethers

174450-50-1	Alcohol, C12-14, ethoxylated, sulfates, triisopropanolamine salts
102783-14-2	Poly(oxy-1,2-ethanediyl), a-sulfo-w-hydroxy-, C10-18-alkyl ethers, sodium salts
9004-82-4	Sodium lauryl ether sulfate
25231-22-5	Poly(oxy-1,2-ethanediyl), .alpha.-[(tridecyloxy)sulfonyl]-.omega.-hydroxy-, sodium salt
34431-25-9	Polyethylene glycol octyl ether sulfate, sodium salt
52286-19-8	Polyethylene glycol decyl ether sulfate, ammonium salt
67762-21-4	Poly(oxy-1,2-ethanediyl), .alpha.-sulfo-.omega.-hydroxy-, C10-16-alkyl ethers, magnesium salts
68081-91-4	Poly(oxy-1,2-ethanediyl), .alpha.-sulfo-.omega.-hydroxy-, C12-18-alkyl ethers, sodium salts
68184-04-3	2-Aminoethanol compd. with .alpha.-sulfo-.omega.-(dodecyloxy)poly(oxy-1,2-ethanediyl) (1:1)
68610-22-0	Poly(oxy-1,2-ethanediyl), .alpha.-sulfo-.omega.-hydroxy-, C12-18-alkyl ethers, ammonium salts
68891-29-2	Poly(oxy-1,2-ethanediyl), .alpha.-sulfo-.omega.-hydroxy-, C8-10-alkyl ethers, ammonium salts
68891-30-5	Poly(oxy-1,2-ethanediyl), .alpha.-sulfo-.omega.-hydroxy-, C11-15-branched alkyl ethers, ammonium salts
73665-22-2	Poly(oxy-1,2-ethanediyl), .alpha.-sulfo-.omega.-hydroxy-, C6-10-alkyl ethers, sodium salts
157627-95-7	Poly(1,2-ethanediyl), .alpha.-sulfo-.omega.-hydroxy-C16-18 and C18 unsaturated alkyl ethers, sodium salts
160104-51-8	Poly(1,2-ethanediyl), .alpha.-sulfo-.omega.-hydroxy-C12-14 alkyl ethers, magnesium salts
160104-52-9	Poly(1,2-ethanediyl), .alpha.-sulfo-.omega.-hydroxy-C16-18 and C18 unsaturated alkyl ethers, magnesium salts
67762-19-0	Poly(oxy-1,2-ethanediyl), .alpha.-sulfo-.omega.-hydroxy-, C10-16-alkyl ethers, ammonium salts
13150-00-0	Ethanol, 2-[2-[2-(dodecyloxy)ethoxy]ethoxy]-, hydrogen sulfate, sodium salt
32612-48-9	Poly(oxy-1,2-ethanediyl), .alpha.-sulfo-.omega.-(dodecyloxy)-, ammonium salt